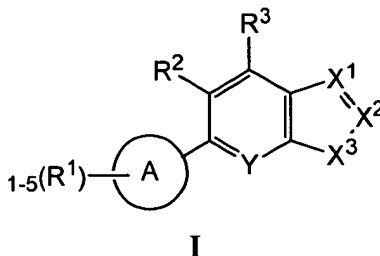


AMENDMENTS MADE TO THE SPECIFICATION

[0024] One aspect of the invention, Example [0024], is a compound for inhibiting ALK according to formula I,



or a pharmaceutically acceptable salt, or stereoisomer, prodrug or metabolite thereof, wherein,

A is a five- to ten-membered ring containing up to three heteroatoms; provided A is not a saturated alicyclic when X² is =N-, X³ is -O-, and A is a pyridin-4-yl;

each of R¹, R² and R³ is independently selected from -H, halo, trihalomethyl, -CN, -NO₂, -OR⁴, -N(R⁴)R⁴, -S(O)₀₋₂R⁴, -SO₂N(R⁴)R⁴, -CO₂R⁴, -C(=O)N(R⁴)R⁴, -C(=O)R⁴, -C(=NR⁵)N(R⁴)R⁴, -C(=NR⁵)R⁴, -N(R⁴)SO₂R⁴, -N(R⁴)C(O)R⁴, -NCO₂R⁴, optionally substituted alkoxy, optionally substituted C₁₋₆ alkyl, optionally substituted aryl, optionally substituted aryl C₁₋₆ alkyl, optionally substituted heterocyclyl, and optionally substituted heterocyclyl C₁₋₆ alkyl;

two adjacent of R¹, together with the annular atoms to which they are attached, can form a five- to six-membered ring containing up to two heteroatoms and optionally substituted with up to four of R¹⁰;

R² and R³, together with the annular atoms to which they are attached, can form a five- to six-membered ring containing up to two heteroatoms and optionally substituted with up to five of R⁶;

each R⁴ is selected from -H, optionally substituted C₁₋₆ alkyl, optionally substituted aryl, optionally substituted aryl C₁₋₆ alkyl, optionally substituted heterocyclyl, and optionally substituted heterocyclyl C₁₋₆ alkyl;

two of R^4 , when taken together with a common nitrogen to which they are attached, form an optionally substituted five- to seven-membered heterocyclyl, said optionally substituted five- to seven-membered heterocyclyl optionally containing at least one additional heteroatom selected from N, O, S, and P;

each R^5 is selected from -H, -CN, -NO₂, -OR⁴, -S(O)₀₋₂R⁴, -CO₂R⁴, optionally substituted C₁₋₆ alkyl, optionally substituted C₂₋₆ alkenyl, and optionally substituted C₂₋₆ alkynyl;

Y is =N- or =C(R⁸)-;

X¹ and X² are each independently either =N- or =C(R⁹)-;

X³ is selected from -N(R⁷)-, -O-, and -S-;

R⁷ is selected from -H, optionally substituted C₁₋₆alkyl, -SO₂N(R⁴)R⁴, -CO₂R⁴, -C(=O)N(R⁴)R⁴, -C(=NR⁵)N(R⁴)R⁴, -C(=NR⁵)R⁴, -C(=O)R⁴, optionally substituted alkoxy, optionally substituted aryl, optionally substituted aryl C₁₋₆ alkyl, optionally substituted heterocyclyl, and optionally substituted heterocyclyl C₁₋₆ alkyl;

each of R⁶, R⁸, R⁹ and R¹⁰ is independently selected from -H, halo, trihalomethyl, -CN, -NO₂, -OR⁴, -N(R⁴)R⁴, -S(O)₀₋₂R⁴, -SO₂N(R⁴)R⁴, -CO₂R⁴, -C(=O)N(R⁴)R⁴, -C(=NR⁵)N(R⁴)R⁴, -C(=NR⁵)R⁴, -N(R⁴)SO₂R⁴, -N(R⁴)C(O)R⁴, -NCO₂R⁴, -C(=O)R⁴, optionally substituted alkoxy, optionally substituted C₁₋₆ alkyl, optionally substituted aryl, optionally substituted aryl C₁₋₆ alkyl, optionally substituted heterocyclyl, and optionally substituted heterocyclyl C₁₋₆ alkyl; provided when R⁹ is aryl, heteroaryl, -C(H)=C(H)R or -C(H)=NR, where R is an optionally substituted alkyl, cycloalkyl, heteroalicyclic, aryl, or heteroaryl, then Y is not =C(H)-; and

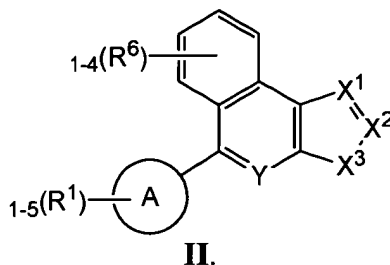
two adjacent of R⁶, together with the annular atoms to which they are attached, can form an optionally substituted five- to seven-membered ring containing up to two heteroatoms.

[0025] In one example [0025], the compound is according to example paragraph [0024], wherein R² and R³, together with the carbons to which they are attached, form a five- to six-membered ring containing up to two heteroatoms and optionally substituted with up to four of R⁶.

[0026] In another example [0026], the compound is according to example paragraph [0025], wherein said five- to six-membered ring is an aryl or a heteroaryl.

[0027] In another example [0027], the compound is according to example paragraph [0026], wherein said five- to six-membered ring is phenyl or pyridyl.

[0028] In another example [0028], the compound is according to example paragraph [0027], of formula II,



[0029] In another example [0029], the compound is according to example paragraph [0028], wherein X^1 is $=C(R^9)-$, X^2 is $=N-$, and X^3 is $=N(R^7)-$.

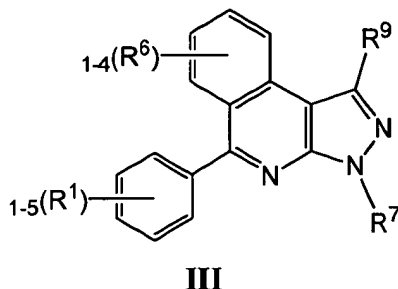
[0030] In another example [0030], the compound is according to example paragraph [0029], wherein Y is $=N-$.

[0031] In another example [0031], the compound is according to example paragraph [0030], wherein A is either a ~~five-six~~-to ten-membered aryl or a five- to ten-membered heteroaryl containing up to three heteroatoms.

[0032] In another example [0032], the compound is according to example paragraph [0031], wherein A is either a ~~five-or-six~~-membered aryl or a five- or six-membered heteroaryl containing up to three heteroatoms.

[0033] In another example [0033], the compound is according to example paragraph [0032], wherein R^1 is selected from -H, halo, trihalomethyl, -CN, -OR⁴, -N(R⁴)R⁴, -SO₂N(R⁴)R⁴, -CO₂R⁴, -C(=O)N(R⁴)R⁴, -C(=NR⁵)N(R⁴)R⁴, -C(=NR⁵)R⁴, -N(R⁴)SO₂R⁴, -N(R⁴)C(O)R⁴, -NCO₂R⁴, optionally substituted alkoxy, optionally substituted C₁₋₆ alkyl, optionally substituted heterocyclyl, and optionally substituted heterocyclyl C₁₋₆ alkyl.

[0034] In another example [0034], the compound is according to example paragraph [0033], of formula III,



wherein at least one of R^1 is -OH.

[0035] In another example [0035], the compound is according to example paragraph [0034], wherein the compound is either a 3-(3H-pyrazolo[3,4-c]isoquinolin-5-yl)-phenol or a 4-(3H-pyrazolo[3,4-c]isoquinolin-5-yl)-phenol.

[0036] In another example [0036], the compound is according to example paragraph [0035], wherein R^9 is selected from -H, trihalomethyl, optionally substituted alkoxy, optionally substituted C_{1-6} alkyl, optionally substituted aryl C_{1-6} alkyl, optionally substituted heterocyclyl, and optionally substituted heterocyclyl C_{1-6} alkyl.

[0037] In another example [0037], the compound is according to example paragraph [0036], wherein R^6 is selected from -H, halo, trihalomethyl, -CN, -OR⁴, -N(R⁴)R⁴, -CO₂R⁴, -C(=O)N(R⁴)R⁴, -N(R⁴)SO₂R⁴, -N(R⁴)C(O)R⁴, -NCO₂R⁴, -C(=O)R⁴, optionally substituted C_{1-6} alkyl, optionally substituted heterocyclyl, optionally substituted heterocyclyl C_{1-6} alkyl, and a six- or seven-membered heteroalicyclic formed by two adjacent of R^6 , together with the annular atoms to which they are attached, said six- or seven-membered heteroalicyclic containing up to two heteroatoms.

[0038] In another example [0038], the compound is according to example paragraph [0037], wherein R^6 is selected from -H, halo, -OR⁴, -N(R⁴)R⁴, optionally substituted C_{1-6} alkyl, optionally substituted heterocyclyl, optionally substituted heterocyclyl C_{1-6} alkyl, and a six- or seven-membered heteroalicyclic formed by two adjacent of R^6 , together with the annular atoms to which they are attached, said six- or seven-membered heteroalicyclic containing up to two heteroatoms.

[0039] In another example [0039], the compound is according to example paragraph [0038], wherein at least one of R⁶ is optionally substituted C₁₋₆ alkoxy.

[0040] In another example [0040], the compound is according to example paragraph [0039], wherein at least one of R¹ is halogen or methyl.

[0041] In another example [0041], the compound is according to example paragraph [0040], wherein R⁹ is selected from -H, trihalomethyl, and optionally substituted C₁₋₆ alkyl.

[0042] In another example [0042], the compound is according to example paragraph [0038], wherein at least one of R⁶ is C₁₋₆ alkoxy substituted with a heteroalicyclic.

[0043] In another example [0043], the compound is according to example paragraph [0042], wherein said heteroalicyclic is selected from the group consisting of dioxolanyl, piperidinyl, piperazinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, 2-oxoazepinyl, azepinyl, 4-piperidonyl, pyrrolidinyl, morpholinyl, quinuclidinyl, tetrahydrofuryl, tetrahydropyranyl, thiamorpholinyl, thiamorpholinyl sulfoxide, 2,5-diaza-bicyclo[2.2.1]heptanyl, and thiamorpholinyl sulfone.

[0044] In another example [0044], the compound is according to example paragraph [0038], wherein at least one of R⁶ is C₁₋₆ alkoxy substituted with at least one additional of an optionally substituted alkoxyl, an amino, an optionally substituted dialkylamino, and an optionally substituted monoalkylamino.

[0045] In another example [0045], the compound is according to example paragraph [0024], selected from Table 1.

On pages 65 of the Specification, please replace paragraph [0089] with the following amended paragraph.

[0089] “Optional” or “optionally” means that the subsequently described event or circumstance may or may not occur, and that the description includes instances where said event or circumstance occurs and instances in which it does not. One of ordinary skill in the art would understand that, with respect to any molecule described as containing one or more optional substituents, that only sterically practical and/or synthetically feasible compounds are meant to be included. “Optionally substituted” refers to all subsequent modifiers in a term, for example in the term “optionally substituted arylC₁₋₈ alkyl,” optional substitution may occur on both the “C₁₋₈ alkyl” portion and the “aryl” portion of the molecule; and for example, optionally substituted alkyl includes optionally substituted cycloalkyl groups, ~~which in turn are defined as including optionally substituted alkyl groups, potentially *ad infinitum*.~~ A list of exemplary optional substitution are listed below in the definition of “substituted.”

Please delete the following from Table 2, entries 1, 2, 4-8, 11, 16-18, 23, 30, 33, 43, 46-53, 56-57, 62, 68, 73-75, 77, 84, 86, 119, 124, 163, 175, 180, 181, 189, 190, 192, 204, 205, 211, 222, and 246 found on pages 170-175, 177-178, 180-184 and 186 of the Specification.